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Effects of nephrectomy on renal salt and water transport in the remaining kidney

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Effects of nephrectomy on renal salt and water transport in the remaining kidney. Fluid, sodium, and potassium transport was studied in proximal and distal tubules in rats in which one kidney had been removed two weeks after a suprarenal aortic clamp had been placed to prevent adaptive changes in glomerular filtration rate (GFR) in the experimental kidney. Free-flow micropuncture techniques were used and tubular fluid (TF) samples analyzed for inulin, sodium and potassium. In addition, peritubular total protein concentrations and luminal and peritubular hydrostatic pressures were measured. The following changes were observed 15 hr after unilateral nephrectomy: (*1*) a significant increase in single nephron GFR; (*2*) unchanged absolute proximal tubular reabsorption rates of fluid and sodium; (*3*) increased delivery of fluid into distal tubules; (*4*) increased distal tubular reabsorption of sodium, but of insufficient magnitude to prevent natriuresis; and (*5*) an augmentation of distal tubular potassium secretion. Reduction of single nephron GFR to control levels by aortic clamping abolished the natriuresis following nephrectomy.

Effets de la néphrectomie sur le transport du sel et de l'eau dans le rein restant. Le transport d'eau, de sodium et de potassium a été étudié dans les tubes proximaux et distaux de rats chez lesquels un rein avait été enlevé deux semaines après qu'un clamp aortique susrénal ait été placé de facon à empêcher les modifications du débit de filtration glomérulaire (GFR) dans le rein expérimental. Les techniques de microponction en flux libre ont été utilisées et les échantillons de liquide tubulaire (TF) ont été analysés pour déterminer les concentrations d'inuline, de sodium et de potassium. De plus, la concentration totale des protéines dans le liquide péritubulaire et les pressions hydrostatiques luminale et péritubulaire ont été mesurées. Le résultats suivants ont été obtenus quinze heures après la néphrectomie unilatérale: *1*) une augmentation significative du débit de filtration des néphrons, *2*) l'absence de modification des débits tubulaires proximaux de réabsorption absolue d'eau et de sodium, *3*) une augmentation du débit d'eau delivré aux tubes distaux, *4*) une augmentation de la réabsorption tubulaire distale du sodium, mais insuffisante pour empêcher une natriurèse et, *5*) une augmentation de la sécrétion tubulaire distale du potassium. La diminution du débit de filtration glomérulaire des néphrons jusqu'á la valeur contrôle au moyen du clamp aortique abolit la natriurèse consécutive à la néphrectomie.

Reduction of renal mass is followed by a rapid increase of urine flow accompanied by marked natriuresis and kaliuresis in the remaining kidney. This adaptative response is fast [1] and may occur without any change in glomerular filtration rate (GFR). It has also been observed in the remaining kidney even when its blood supply has been restricted, a situation in which sodium and water excretion are markedly depressed prior to unilateral nephrectomy [2].

The present study was done, first, to pin-point the sites along the nephron where functional changes in fluid, sodium, and potassium transport take place 15 hr after unilateral nephrectomy. Secondly, an attempt was made to define the participation of some physical factors, such as peritubular hydrostatic and oncotic pressure, and some renal hemodynamic factors in the adaptive response.

Our results indicate that 15 hr after nephrectomy arterial blood pressure and the delivery of filtrate into the distal tubules in the remaining kidney of superficial nehprons increase uniformly. Despite a significant increase in single nephron filtration rate, achieved at constant filtration fraction, proximal tubular reabsorption of sodium continued at an unaltered absolute rate and resulted in the delivery of larger than normal quantities of fluid into the distal nephron. This redistribution of glomerular filtrate from proximal to distal nephron sites was associated with natriuresis and accelerated distal tubular secretion of potassium. Reduction of single nephron filtration rate by aortic clamping to levels slightly below control abolished the natriuresis following contralateral nephrectomy.

Methods

Preparation of animals. Male, Long-Evans rats ranging in wieght from 180 to 300 g were used. The animals had free access to food until the night preceding the experiment; water was given *ad lib.* Ten to 15 days before the micropuncture experiments, aortic clamps were placed, under ether anesthesia, between the origin of the two renal arteries. The silver clamps were similar to those described by Pickering and Prinzmetal [3], the inner width being set at 0.25 mm. The clamps were tightened *in situ* as much as pos-

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sible, with care being taken to avoid ischemia of the left kidney as judged by visual inspection. Ten to 15 days later, and 15 hr before the micropuncture experiments, either a right nephrectomy (1/2 Nex group) or a sham operation (control group) was performed under ether anesthesia.

Since we observed that unilaterally nephrectomized animals had arterial blood pressure levels moderately but significantly higher than control animals, an additional group of unilaterally nephrectomized rats was prepared in which the renal arterial pressure was acutely reduced prior to the collection of tubular samples. An adjustable aortic constriction device was used and the aortic pressure reduced by 20 to 30 mm Hg.

An additional group of five unilaterally nephrectomized animals was infused with Ringer's solution (see following) containing aldosterone (0.25μg/min). Whole kidney GFR and electrolyte excretion were measured in these rats 90 min after the infusion was begun.

Anesthesia was induced by slow i.v. infusion of sodium pentobarbital (Diabutal®, 30 to 50 mg/kg of body wt) into a lateral caudal vein. The animal was placed on a heated table and a tracheotomy was performed; the right jugular vein was cannulated with two PE-10 polyethylene catheters, one being used for the infusion of saline solution, the other for lissamine green injection. The left femoral artery was catheterized with PE-50 polyethylene tubing for measurements of arterial blood pressure and blood sampling. The left kidney was exposed by flank incision, freed from its connective tissue attachments and placed in a Lucite holder covered with mineral oil kept at 37°C. In the control group in which both kidneys were present, the urinary bladder was cannulated and urine collected for the functional assessment of the right unexposed kidney. The ureter of the punctured kidney was cannulated with PE-50 polyethylene tubing.

Micropuncture experiments. During the micropuncture experiments, rats were infused with Ringer's solution (143 mM Na, 4 mM K, 122 mM Cl, 25 mM HCO_3) at a rate of 50μl/min. Both control and ½ Nex animals received a priming infusion containing, in a volume of 0.6 ml, 4 g/100 ml of inulin (Pfanstiehl Lab. Inc., Waukegan, IL) and, whenever plasma flow was measured, in addition 120 mg/100 ml of para-aminohippurate (PAH, Sigma Chemical Co.). The sustaining infusion contained 3.6 g/100 ml of inulin and 350 mg/100 ml of PAH in control, and 2 g/100 ml and 180 mg/100 ml of PAH in unilaterally nephrectomized rats. The latter concentrations were chosen to avoid inordinately high inulin and PAH concentrations in the unilaterally nephrectomized group of animals.

Tubular fluid was collected from superficial proximal and distal tubules by methods described previously [4]. Each animal received a single injection of lissamine green (0.05 ml of a 5% phosphate-buffered solution) for measurement of transit time and for the identification of distal tubules on the kidney surface.

Tubular fluid samples were collected with sharpened glass micropipets (O.D., 8 to 14μm), filled with Sudan-black-colored mineral oil. After tubular impalement a small oil droplet was injected to delineate direction of flow and, subsequently, a larger drop (between 3 and 6 tubular diameters) was injected. It was kept distal to the puncture site to avoid retrograde collection. After gentle suction was applied, tubular fluid entered freely into the collecting pipet. Collection time was at least three minutes; sample size ranged from 20 to 130 nl. Volume measurements of tubular fluid samples were done with constriction micropipets.

To measure protein concentrations in peritubular plasma, efferent arterioles were punctured with sharpened micropipets (O.D., 8 to 10μm) which had been treated with Desicote® (Beckman). After centrifugation (10 min at 800 $\times$ *g*), plasma was withdrawn and kept under oil for the measurement of total protein concentrations.

Hydrostatic pressure measurements in tubules and capillaries were performed using the Landis method [5]. Sharpened micropipets with an O.D. of 8 to 10μm were used. They were filled with lissamine green-colored isotonic saline and connected to a water manometer. Care was taken to avoid larger infusions of saline into tubules or capillaries during the pressure measurements. Readings were taken when the interface between the colored saline and tubular fluid (or blood) had stabilized within a short distance from the pipet tip.

Analytical methods. Inulin concentrations in blood, urine, and tubular fluid were measured using the fluorimetric method of Vurek and Pegram [6]. The concentration of protein in arterial and peritubular capillary plasma was measured with the technique of Lowry et al [7], as adapted for the use of microsamples by Brenner et al [8]. A bovine albumin solution (Crystallized Bovine Plasma Albumin, Armour Pharmaceutical Co., Chicago, IL) was used as standard in a concentration range from 0 to 12 g/100 ml. Estimates of the filtration fraction were derived from the following formula: FF = 1 − (prot. art./prot. cap.). PAH concentrations in plasma and urine were measured using the method of Smith et al [9]. Na and K concentrations in proximal and distal tubular fluid

Table 1. Summary data in control rats with chronic interrenal aortic clamp

Rat No.	Urine flow $\mu l/kg \cdot min$		GFR $ml/kg \cdot min$		U/P_{In}		P_{Na^+}	P_{K^+}	U/P_{Na^+}		U/P_{K^+}		FE_{Na^+} %filt		FE_{K^+} %filt		$U_{Na^+} \cdot V$ $\mu Eq/kg \cdot min$		$U_{K^+} \cdot V$ $\mu Eq/kg \cdot min$	
	Left	Right	Left	Right	Left	Right	mEq/liter	mEq/liter	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
1	37.7	18.5	6.1	8.1	161.8	437.8	142.9	4.59	0.67	1.04	24.6	48.6	8.51	0.35	14.7	13.2	3.7	3.2	4.3	4.3
2	4.1	30.4	1.9	10.4	463.4	342.1	146.1	4.36	0.46	0.85	15.0	85.4	0.10	0.24	3.3	25.1	0.3	3.8	0.3	11.3
3	13.3	13.3	5.8	6.3	436.1	473.7	142.4	3.88	0.41	0.37	104.6	103.7	0.10	0.09	23.7	22.6	0.8	0.8	5.3	5.3
4	23.3	20.8	4.8	6.3	206.0	302.9	148.7	3.90	0.29	0.61	18.0	63.2	0.15	0.20	8.8	21.0	1.0	1.9	1.6	5.2
5	15.3	15.7	5.1	4.8	333.3	305.7	147.5	3.85	0.39	0.51	65.0	70.5	0.12	0.16	19.5	23.0	0.9	1.2	3.8	4.3
6	25.0	26.5	3.2	7.8	128.0	294.3	141.5	3.90	0.68	1.24	46.9	82.5	0.53	0.43	36.7	27.8	2.4	4.9	4.6	8.5
7	26.8	49.5	6.1	6.6	227.6	133.3	142.2	3.94	—	—	26.6	26.6	—	—	12.6	19.4	—	—	2.9	5.0
8	9.8	19.9	5.0	5.0	510.2	251.3	144.3	4.85	1.68	1.34	24.8	20.5	0.03	0.74	10.3	17.5	0.2	2.3	2.4	4.3
9	8.8	10.2	5.3	5.5	602.3	539.2	145.1	4.25	0.10	0.10	61.0	65.4	0.02	0.02	10.0	12.7	0.1	0.1	2.3	2.0
10	29.7	28.1	5.7	5.2	191.9	185.1	146.9	4.20	0.88	0.56	46.5	45.0	0.46	0.30	24.2	24.5	3.9	2.3	5.7	5.2
11	19.8	21.3	5.7	4.8	287.9	225.4	143.6	4.15	1.30	0.74	44.6	58.0	0.45	0.33	15.3	26.2	4.0	2.4	3.7	5.3
12	29.6	16.2	3.8	6.5	128.4	401.2	143.5	4.20	0.40	0.08	44.1	82.6	0.31	0.02	33.1	20.8	1.7	0.2	5.4	5.7
13	23.4	20.2	5.0	4.2	179.5	207.9	144.0	4 08	1.01	0.84	43.1	48.2	0.58	0.49	21.9	24.7	3.4	2.5	4.1	3.9
14	14.5	37.8	4.1	6.4	283.1	169.8	—	—	—	—	—	—	—	—	—	—	—	—	—	—
15	13.7	30.8	3.9	6.2	280.6	200.4	143.9	3.42	0.15	0.31	76.0	66.0	0.06	0.15	27.2	33.3	0.3	1.4	3.5	7.0
16	16.5	16.8	5.8	5.0	352.5	299.1	142.2	3.49	0.54	0.65	74.9	101.8	0.17	0.27	21.6	41.4	1.3	1.6	4.3	6.1
Mean	19.5	23.5	4.8	6.2	298.3	298.1	144.3	4.07	0.64	0.66	47.7	64.6	0.26	0.27	18.9	23.5	1.7	2.1	3.6	5.6
SEM	2.3	2.5	0.3	0.4	35.5	29.1	0.6	0.10	0.12	0.10	6.5	6.3	0.06	0.05	2.4	1.9	0.4	0.4	0.4	0.6
N	16	16	16	16	16	16	15	15	14	14	15	15	14	14	15	15	14	14	15	15
			<0.01								*NS*									

Table 2. Summary data in the remaining kidney in rats with interrenal aortic clamps and chronic contralateral nephrectomy

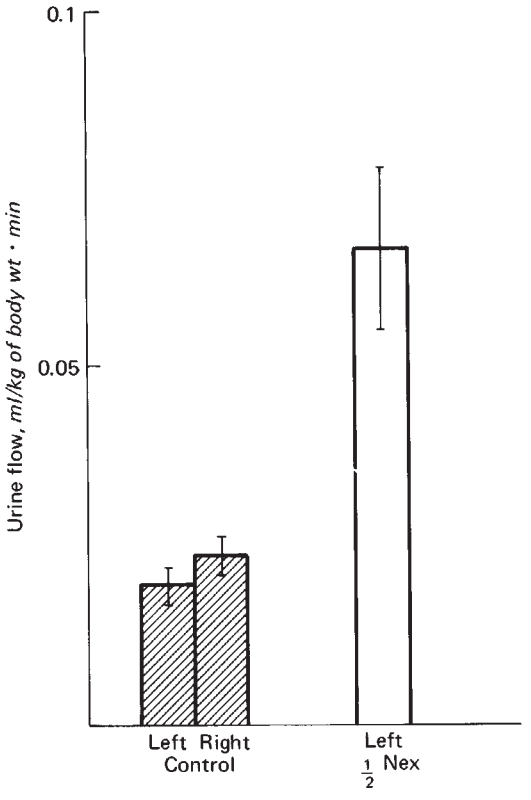
Rat No.	Urine flow *μl/kg·min*	GFR *ml/kg·min*	U/P_{In}	P_{Na+} *mEq/liter*	P_{K+} *mEq/liter*	U/P_{Na+}	U/P_{K+}	FE_{Na} *%filt* (× 100)	FE_K *%filt* (× 100)	$U_{Na+}\cdot V$ *μEq/kg·min*	$U_K + V$ *μEq/kg·min*
1	161.0	1.4	8.7	146.5	5.08	0.91	8.5	10.4	96.5	21.6	6.8
2	37.8	5.9	156.1	144.4	4.27	0.89	21.7	0.66	13.8	5.9	3.5
3	51.1	2.3	45.0	144.8	4.29	0.87	25.8	1.91	55.4	6.5	5.6
4	60.0	6.8	113.3	144.5	4.69	1.03	23.7	0.91	20.1	9.0	6.5
5	38.8	6.2	159.8	143.5	4.27	0.53	34.0	0.33	21.2	3.0	6.8
6	42.3	4.7	111.1	148.2	4.81	0.81	30.2	0.75	27.6	5.3	6.2
7	56.5	6.4	113.3	142.7	4.06	0.46	35.0	1.53	30.9	14.0	8.0
8	47.5	4.6	96.8	140.3	4.40	0.13	53.0	1.54	23.8	10.0	4.7
9	45.4	1.4	30.8	139.0	4.10	0.65	24.4	2.25	76.2	4.9	4.5
10	32.3	4.0	123.8	147.6	3.94	1.89	47.7	1.51	38.1	9.1	6.1
11	19.2	5.1	265.1	141.7	3.93	0.70	63.5	0.27	24.0	4.8	4.8
12	72.7	6.2	85.3	146.4	4.57	0.55	28.6	0.62	33.3	5.6	9.5
13	132.4	6.6	49.8	141.7	4.56	0.98	17.2	1.68	28.0	13.2	8.4
14	168.6	6.4	37.8	143.5	3.89	1.19	—	3.15	—	28.8	—
15	55.0	4.5	86.6	146.0	4.34	0.55	24.1	0.71	28.4	5.1	5.6
16	38.9	4.6	116.1	144.3	3.99	1.28	44.7	1.10	38.8	7.4	6.8
Mean	66.2	4.8	100.0	144.1	4.32	0.83	32.1	1.83	37.1	9.6	6.3
SEM	11.4	0.4	15.6	0.6	0.08	0.10	3.8	0.60	5.8	1.7	0.4
N	16	16	16	16	16	16	15	16	15	16	15

were measured by dual channel ultramicroflame photometry [10], and in urine and plasma with a flame photometer (Instrumentation Laboratory, model 143). The difference between means of urinary and plasma concentrations, excretion rates and tubular fluid/plasma concentration ratios were evaluated by the *t* test and the data expressed as mean values ± SEM.

Results

Whole kidney function. Data on overall kidney function in control (both kidneys present) and in unilaterally nephrectomized (½ Nex) rats are summarized in Tables 1 and 2. A comparison of the values of GFR and urinary water and electrolyte excretion between the two groups (control and unilaterally nephrectomized) indicates the following: *1*) The chronic presence of an interrenal aortic clamp led to a moderate but statistically significant ($P < 0.01$) reduction of kidney GFR of the clamped (left) kidney although the difference in GFR was quite variable. *2*) Removal of the right kidney did not affect the total GFR of the remaining clamped kidney (compare Tables 1 and 2; see also Fig. 1). The range of GFR 15 hr after contralateral nephrectomy showed similar variations as in the control group. Urinary excretion data indicate that urine flow rates as well as fractional and absolute Na and K excretion rates were slightly lower in the clamped left kidney of control rats (Table 1, Figs. 1, 2 and 3) but these differences reached statistical significance ($P < 0.01$) only with respect to absolute rates of urinary potassium excretion. *3*) Removal of the right kidney led to a marked elevation or urine flow and fractional and absolute excretion rates of Na and K in the remaining kidney (Tables 1 through 4; Figs. 1 through 4). Compared to control kidneys at similar GFR levels (see Table 3), the effect of unilateral nephrectomy was most striking when the GFR of the remaining kidney had been significantly lowered by the application of the interrenal clamp. The data presented in Table 3 and Figure 4 indicate that the increase in fractional Na and K excretion was most dramatic when the excretion patterns of control and ½ Nex kidneys were compared at similarly low absolute GFR values. However, even at moderately low or normal GFR values, the diuretic, natriuretic and kaliuretic effects of unilateral nephrectomy were still present.

A consistent finding in the present series of experiments was that measurements of femoral arterial blood pressure were significantly higher ($P< 0.05$) in ½ Nex rats (119 ± 5 mm Hg) than in control animals (101 ± 5 mm Hg). To test whether this change of arterial blood pressure was involved in the diuretic response of the remaining kidney after contralateral nephrectomy, in seven additional unilaterally nephrectomized animals an adjustable periaortic clamp was used to decrease the perfusion pressure of the left renal artery at the beginning of the micropuncture experiment. In this group of animals, mean femoral blood pressure was initially 125 ± 2 mm Hg, and was reduced to a mean value of 90 ± 2 mm Hg. Inspection of Table 5 shows that this maneuver did not decrease overall kidney GFR (mean control value, 4.8 ± 0.4 ml/kg · min · kidney; mean value after application of aortic clamp; 4.7 ± 0.4 ml/kg · min · kidney) but that it nevertheless significantly depressed fractional and absolute excretion rates of so-



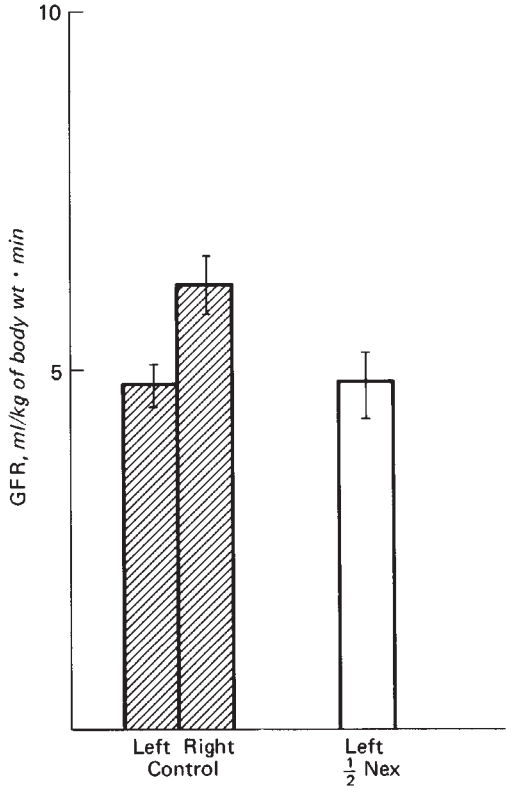
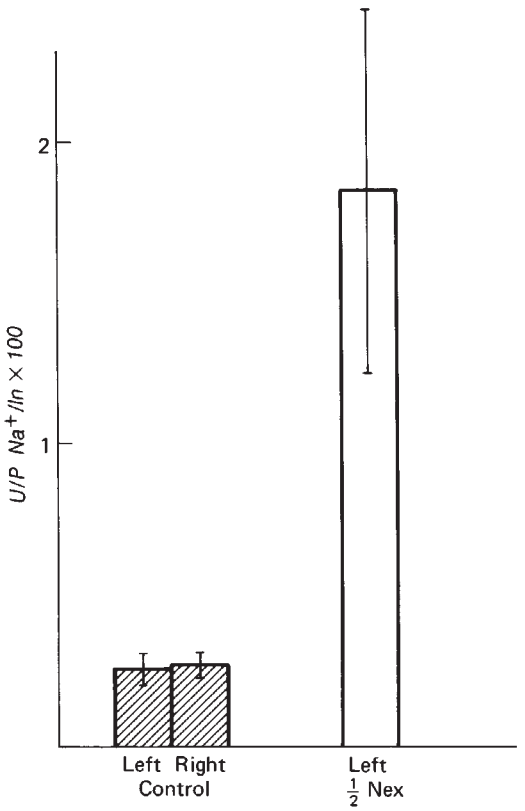


Fig. 1. *Summary of mean urine flow rates and GFR in control and ½ nephrectomized animals.* Length of bar indicates ± SEM.



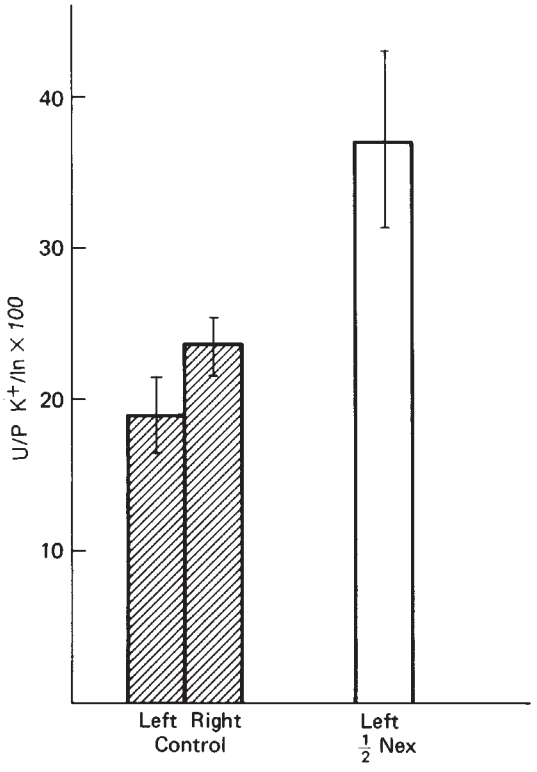


Fig. 2. *Summary of mean fractional excretion rates of Na^+ and K^+ in control and ½ nephrectomized animals.*

dium from a mean value of 9.6 ± 1.7 to 2.8 ± 0.7 μEq/kg · min.

The natriuretic response to unilateral nephrectomy was not affected by i.v. administration of aldosterone. For similar ranges of GFR values (5.2 ± 0.3 ml/min · kg, $N = 9$), absolute excretion of Na during aldosterone infusion was 8.9 ± 0.6μEq/min·kg, and the urine flow was 43.5 ± 2.8μl/min·kg. These values are not significantly different from those measured in ½ Nex without exogeneous aldosterone.

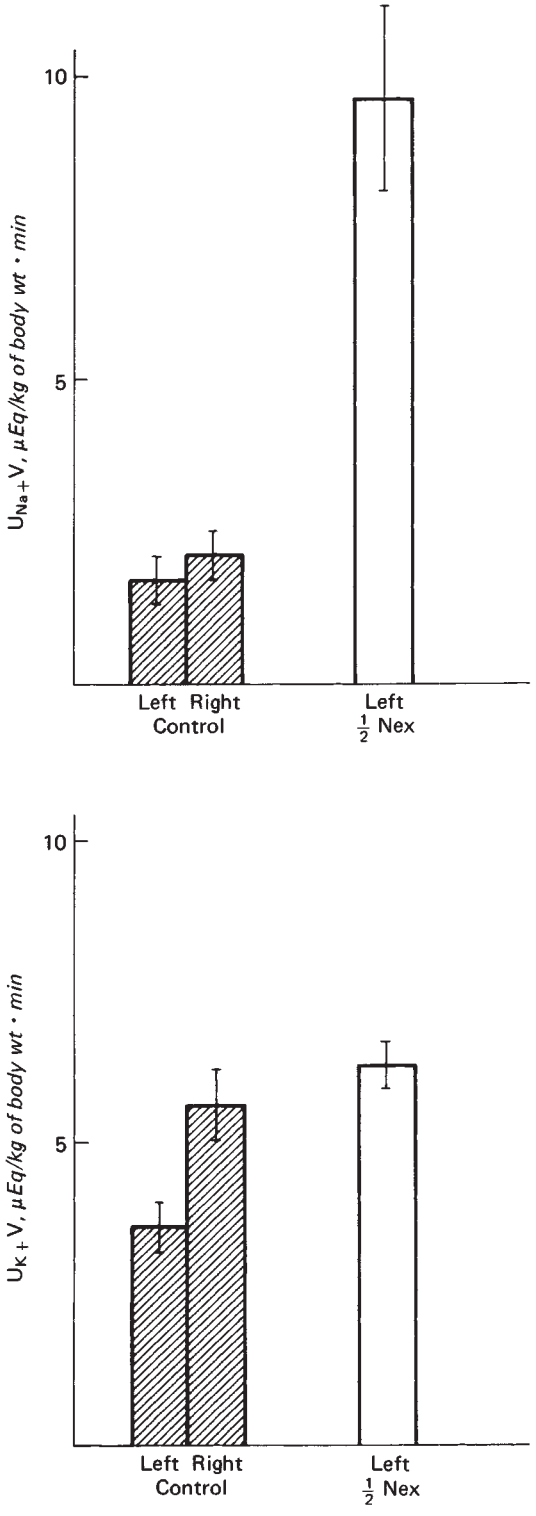


Fig. 3. *Summary of mean absolute excretion rates of Na and K in control and ½ nephrectomized animals.*

Tubular micropuncture experiments. A comparison of single nephron glomerular filtration rates (SNGFR) between control and unilaterally nephrectomized animals shows significant differences. SNGFR was significantly ($P < 0.01$) higher (53.2 ± 2.0 nl/min) in ½ Nex than in control animals (44.3 ± 2.7 nl/min). A suggestive, albeit not statistically significant, positive correlation was found between whole kidney GFR and mean SNGFR of individual kidneys in both control and unilaterally nephrectomized animals. Fractional reabsorption of fluid was less in ½ Nex than in control animals (see following); absolute fluid reabsorption in proximal tubules did not differ between the two groups (mean values: 19.4 ± 1.3 nl/min in ½ Nex, 20.6 ± 2.0 in control animals). After clamping of the aorta above the left renal artery in unilaterally nephrectomized rats, SNGFR decreased to a mean value of 46.7 ± 1.5 nl/min, a value significantly lower than that measured in unilaterally nephrectomized rats without aortic clamping. Absolute fluid reabsorption along the proximal tubule was 22.2 ± 0.6 nl/min, not different from that in control and ½ Nex rats.

Fig. 5 summarizes proximal and distal tubular inulin data in control and ½ Nex animals. Fluid reabsorption was depressed in unilaterally nephrectomized animals, since tubular fluid to plasma (TF/P) inulin ratios are generally lower along both the proximal and distal tubule. Similarly, mean inulin U/P ratios are significantly depressed in ½ Nex rats. Mean late proximal TF/P inulin ratios (60 to 95% of proximal convoluted tubule) were 1.60 ± 0.05 in ½ Nex rats, significantly less ($P < 0.001$) than the mean value of 1.95 ± 0.08 in control rats. Clamping of the aorta above the origin of the renal arteries led to an increase in late proximal TF/P ratio to a mean of 1.98 ± 0.08, a value nearly identical to that in control animals.

Similar to proximal tubular inulin concentration ratios, late distal inulin ratios were also reduced in ½ Nex rats. The mean values (80 to 100% distal tubule length) were 8.3 ± 1.3 in ½ Nex rats as compared to a mean value of 14.8 ± 1.5 in control animals. These values are significantly different from each other ($P < 0.01$).

A comparison of the concentration profile of sodium along superficial tubules also showed some differences between control and unilaterally nephrectomized animals. Proximal sodium TF/P ratios did not

Table 3. Comparison of fractional urinary Na^+ and K^+ excretion in groups of control and ½ Nex rats with similar ranges of GFR[a]

	GFR: 1 to 2.9 ml/kg · min		GFR: 3 to 4.9 ml/kg · min		GFR: > 5 ml/kg · min	
	½ Nex	Control	½ Nex	Control	½ Nex	Control
GRF *ml/kg·min*	1.7 ± 0.1 (3)	1.9 (1)	4.4 ± 0.2 (5)	3.9 ± 0.3 (5)	6.3 ± 0.5 (8)	5.6 ± 0.2 (10)
$U/P_{Na^+/In}$ *× 100*	5.1 ± 1.3 (3)	0.1 (1)	1.1 ± 0.1 (5)	0.26 ± 0.07 (4)	1.2 ± 0.2 (8)	0.26 ± 0.06 (9)
$U/P_{K^+/In}$ *× 100*	77.9 ± 5.5 (3)	3.3 (1)	30.7 ± 1.9 (5)	26.5 ± 4.1 (4)	24.8 ± 1.8 (7)	17.7 ± 1.3 (10)

[a] Mean values ± SEM. The number of animals is indicated in parenthesis. Only values of *left* kidneys of control rats with interrenal clamps are given.

differ from unity in either group of animals (mean value of 1.02 ± 0.01 in control and 1.02 ± 0.01 in ½ Nex animals), but due to the lower rate of fractional proximal tubular fluid reabsorption in ½ Nex animals, the fractional excretion of sodium at the end of the proximal tubule (0.66 ± 0.02) was significantly higher ($P < 0.005$) than the mean control value of 0.55 ± 0.02. Fig. 6 summarizes distal tubular sodium data. Inspection of tubular sodium TF/P ratios shows a marked difference in that these values failed to decline as a function of tubular length in the unilaterally nephrectomized animals. It was also apparent that the amount of sodium remaining within the distal tubule lumen was higher in uninephrectomized than in control rats. Since filtration rate is also elevated in these animals, the absolute rate of reabsorption is increased in ½ Nex rats, but not sufficiently to prevent natriuresis. The following absolute rates of Na reabsorption along superficial distal tubules were obtained: 0.57 nEq/min in control rats, as compared to 1.15 nEq/min in ½ Nex animals.[1]

[1] The calculations of absolute rates of sodium reabsorption and potassium secretion along distal tubules were made from the extrapolated values of Na/In and K/In (see Figs. 6 and 7), to 0 and 100% length, and the mean SNGFR values derived from distal tubular collections. The following mean values were obtained: *Sodium:* entry into distal tubule: 0.64 nEq/min (control), 1.36 nEq/min (½ Nex); end-distal values: 0.07 nEq/min (control), 0.21 nEq/min (½ Nex). *Potassium:* entry into distal tubule: 15.1 pEq/min (control), 20.3 pEq/min (½ Nex); end-distal values: 25.4 pEq/min (control), 42.7 pEq/min (½ Nex).

A consideration of tubular potassium data permits the following conclusions: First, transepithelial potassium concentration differences across the proximal tubular epithelium were slightly lower in unilaterally nephrectomized rats (mean TF/P ratio: 0.89 ± 0.02) than in control rats (mean TF/P ratio: 0.97 ± 0.03), a difference which is statistically significant ($P < 0.05$). Second, end-proximal mean fractional excretion rates of potassium did not differ in the two experimental situations (56% in control versus 57% in ½ Nex rats). This finding is of interest since it demonstrates a dissociation between proximal tubular sodium and potassium transport rates at the proximal tubular level. A similar observation has been made after acetazolamide (Diamox®) administration, a situation in which proximal tubular sodium movement is significantly depressed in the presence of continued normal rates of tubular potassium reabsorption [11]. Third, tubular TF/P ratios of potassium along the distal tubule (see Fig. 7) were not different in control and ½ Nex rats. These ratios increased in both control and unilaterally nephrectomized animals from values below unity at early distal tubular sites to values above 2.0 at late distal tubular sites. Fourth, nevertheless, due to the significant lowering of TF/P inulin ratios at the beginning of this nephron segment, a slightly larger potassium load is present at the beginning of the distal tubule in ½ Nex rats than in control animals. Also, a higher rate of potassium

Table 4. Summary data in the remaining kidney in rats with chronic interrenal clamps and contralateral nephrectomy[a]

Rat No.	Urine flow *µl/kg · min*	GFR *ml/kg · min*	U/P_{In}	P_{Na^+} *mEq/liter*	P_{K^+} *mEq/liter*	U/P_{Na^+}	FE_{Na^+} *%filt*	FE_{K^+} *%filt*	$U_{Na^+} \cdot V$ *µEq/kg · min*	U/P_{K^+}	$U_{K^+} \cdot V$ *µEq/kg · min*
1	25.4	4.3	169.3	143.7	4.20	0.71	0.44	37.4	2.6	63.0	6.7
2	21.0	6.1	290.5	144.8	4.23	0.23	0.08	29.2	0.7	84.5	7.4
3	22.8	4.4	193.0	144.1	3.94	0.46	0.29	36.6	1.7	65.2	6.1
4	50.5	3.7	73.3	145.7	4.06	0.40	0.60	58.7	2.9	42.1	8.0
5	26.6	3.7	139.1	142.5	4.17	0.35	0.23	25.9	1.3	35.6	3.9
6	57.5	4.6	80.0	142.9	4.27	0.48	0.62	35.9	3.9	27.6	6.8
7	61.8	6.4	103.6	144.7	3.99	0.74	0.71	32.0	6.6	29.2	8.8
Mean	37.9	4.7	149.8	144.1	4.12	0.48	0.42	36.5	2.8	49.6	6.8
SEM	6.7	0.4	28.9	0.4	0.04	0.07	0.08	4.0	0.7	8.2	0.6
N	7	7	7	7	7	7	7	7	7	7	7

[a] Femoral blood pressure was reduced by a periaortic clamp.

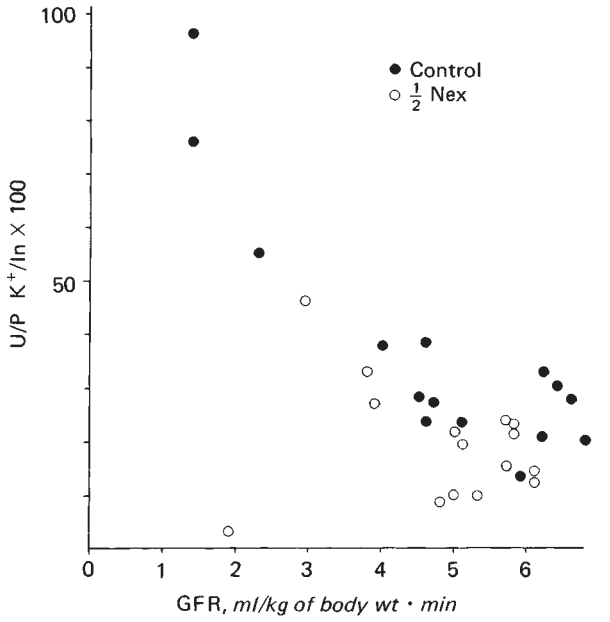


Fig. 4. *Relationship between GFR and fractional excretion rates of K^+ in control and ½ nephrectomized animals.*

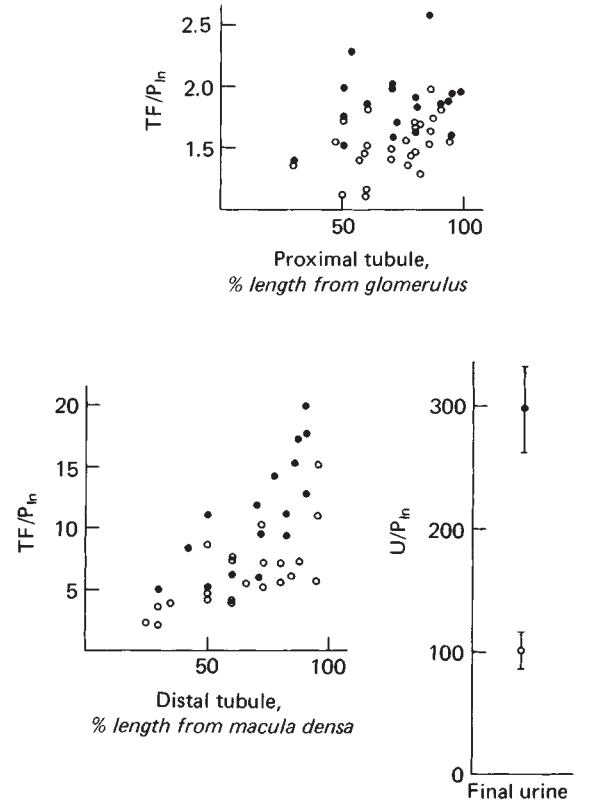


Fig. 5. *Inulin TF/P concentration ratios as function of proximal and distal tubular length.* Urinary concentration ratios (mean ± SEM) are included for comparison. *Open circles* = unilateral nephrectomy; *Solid dots* = control animals.

secretion was maintained along the distal tubule in unilaterally nephrectomized rats. The mean absolute rate of potassium secretion along distal tubules of control rats was 10.3 pEq/min, as compared to 22.4 pEq/min in ½ Nex animals (see footnote 1 on preceding page). This stimulation of potassium secretion was due to larger distal fluid and sodium delivery rather than to the establishment of steeper than normal transepithelial concentration differences. Finally, comparison of late distal with final urinary fractional excretion data indicates that potassium secretion was slightly accentuated along nephron sites beyond the late distal tubule in ½ Nex rats. tion which was mainly responsible for the marked kaliuresis in the unilaterally nephrectomized group of animals.

The absolute amounts of fluid, sodium and potassium entering the loop of Henle were clearly enhanced by unilateral nephrectomy. The absolute amounts of fluid and solutes leaving the proximal convoluted tubule in control and ½ Nex rats were, respectively: Na^+: 3.5 ± 0.2 nEq/min; K^+: 98.7 ± 8.1 pEq/min; fluid: 24.1 ± 1.7 nl/min; and Na^+: 5.0 ± 0.3 nEq/min; K: 129 ± 7.5 pEq/min; and fluid: 33.5 ± 1.7 nl/min.

It is apparent that removal of the contralateral kidney results in a "downward" shift of fluid delivery from the proximal convolution into the distal tubule. Similar to the situation in saline diuresis [12], the resulting relative increase in distal tubular sodium reabsorption is less than the augmentation of distal load and results in natriuresis. With respect to potassium, the situation is also similar to that seen during

Table 5. Comparison of absolute excretion rates of Na^+ and K^+ in groups of control and ½ Nex rats with similar GFR[a]

	GFR: 1 to 2.9 ml/kg·min		GFR: 3 to 4.9 ml/kg·min		GFR: > 5 ml/kg·min	
	½ Nex	Control	½ Nex	Control	½ Nex	Control
GFR, *ml/kg · min*	1.7 ± 0.1 (3)	1.9 (1)	4.4 ± 0.2 (5)	3.9 ± 0.3 (5)	6.3 ± 0.1 (8)	5.6 ± 0.1 (10)
$(U_{Na^+}) \cdot V$, *μEq/kg · min*	11.4 ± 2.7 (3)	0.3 (1)	6.6 ± 0.9 (5)	1.4 ± 0.5 (4)	10.7 ± 1.8 (8)	2.0 ± 0.6 (9)
$(U_{K^+}) \cdot V$, *μEq/kg · min*	5.6 ± 0.4 (3)	0.3 (1)	5.8 ± 1.3 (5)	3.8 ± 0.8 (4)	6.7 ± 0.6 (7)	3.9 ± 0.4 (10)

[a] Mean values ± SEM. The number of animals is indicated in parenthesis. Only values of left kidneys of control rats with interrenal clamps are given.

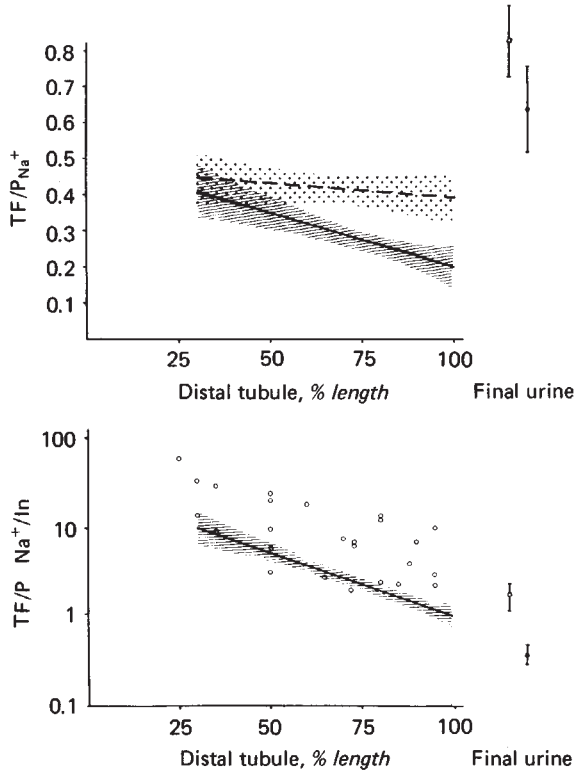


Fig. 6. *Tubular fluid/plasma concentration ratios and fractional excretion rates of Na^+ as function of distal tubular length.* Urinary concentration ratios (mean ± SEM) are included for comparison. *Upper panel: solid* (control) and *broken* (½ Nex) *lines* are linear regressions, *shaded areas* represent 95% confidence limits. *Open* and *solid circles* refer to U/P Na ratios in the final urine. *Lower panel: Open circles:* ½ Nex animals, *solid line:* linear regressions for control values of TF/P Na/In ratios with 95% confidence limits.

saline diuresis [14] and that after administration of those diuretics which inhibit fluid and salt reabsorption at the proximal tubular level or along the ascending thick limb of Henle's loop [15]: increased fluid and sodium delivery, in the presence of well maintained and unchanged luminal potassium concentrations despite a brisk enhancement of volume flow, augment distal tubular potassium secretion and thus lead to marked kaliuresis.

Hemodynamic results. Table 6 summarizes data of total kidney PAH and inulin clearances as well as values of filtration fractions. The latter value was also calculated for superficial nephrons from values of peritubular and arterial plasma protein levels. Arterial plasma protein concentrations (200 to 250 min after starting the saline infusions) were 5.8 ± 0.3 g/100 ml in control, 5.75 ± 0.2 g/100 ml in ½ Nex, and 4.9 ± 0.3 g/100 ml in ½ Nex rats in which aortic pressure had been acutely reduced prior to the micropuncture experiment to levels slightly below but comparable to that in control rats. The absolute level of peritubular protein concentrations was quite similar in the three experimental situations.

Renal blood flow levels in the different experimental conditions are also summarized in Table 6. It is apparent that effective renal blood flow levels were not undergoing significant changes during the different experimental maneuvers. Acute aortic clamping reduced PAH clearance values moderately. Filtration fraction increased after acute aortic clamping but the calculated increase was larger when derived from peritubular protein concentrations (cortical filtration fraction) than when calculated from total renal inulin and PAH clearances (total renal filtration fraction).

Mean proximal tubular hydrostatic pressure averaged 17.6 ± 0.3 cm of H_2O in control animals, and 18.0 ± 0.5 cm of H_2O in ½ Nex animals, values not significantly different from each other. Mean capillary hydrostatic pressure in control rats averaged 12.1 ± 0.6 cm of H_2O, and in unilaterally nephrectomized rats, 14.3 ± 0.5 cm of H_2O. These two values are significantly different from each other ($P < 0.05$).

Arterial hematocrit was 38.8 ± 0.8% in ½ Nex and 40.7 ± 0.6% in control rats, values not significantly different from each other. Assuming constant red cell volume, these hematocrit values suggest that unilat-

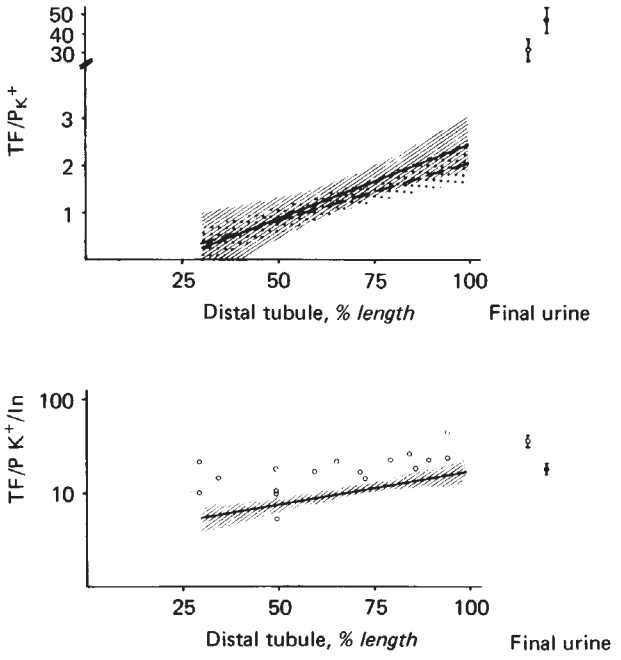


Fig. 7. *Tubular fluid/plasma concentration ratios and fractional excretion rates of K^+ as function of distal tubular length.* Urinary data are included for comparison. *Upper panel: solid* (control) and *broken* (½ Nex) *lines* are linear regressions, *shaded areas* represent 95% confidence limits. *Open* and *solid circles* refer to U/P K^+ ratios in the final urine. *Lower panel: Open circles* represent unilaterally nephrectomized animals; *solid line* represents linear regression for control values of TF/P K/In ratios with 95% confidence limits.

Table 6. Summary of hemodynamic data in different groups of control and experimental animals[a]

	Control	½ Nex	½ Nex + Acute clamp
C_{PAH}, *ml/min · kg · kidney*	15.2 ± 1.1 (5)	17.1 ± 0.7 (5)	13.6 ± 0.6 (7)
C_{In}, *ml/min · kig · kidney*	4.6 ± 0.4	5.6 ± 0.3	4.9 ± 0.3
Kidney FF, × *100*	31.5 ± 2.9	32.4 ± 0.9	35.0 ± 1.2
Capill. prot., *g/100 ml*	8.2 ± 0.6 (5)	8.0 ± 0.2 (7)	7.9 ± 0.3 (7)
Superficial cortical FF, × *100*	30.9 ± 4.1	29.8 ± 2.9	37.1 ± 2.5

[a] Mean values ± SEM. The number of animals is indicated in parenthesis. Only values of *left* kidneys of control rats with interrenal clamps are given.

eral nephrectomy was not associated with larger extracellular volume increments during the administration of i.v. fluid loads.

Urea nitrogen. Blood urea nitrogen levels were measured in four control and in six ½ Nex rats. The mean value in control animals was 15.5 ± 1.2 mg/100 ml, and 28.5 ± 4.6 mg/100 ml in unilaterally nephrectomized rats. As expected, higher blood urea values were found in those animals in which GFR was most markedly depressed.

Discussion

The most striking finding of the present study was the development of a significant reduction in fractional proximal tubular sodium and fluid reabsorption in the remaining clamped kidney after contralateral nephrectomy. Our observations confirm and extend the findings by others that reduction of functional renal mass, achieved either by contralateral nephrectomy [16,17], by surgical ablation [18], or by partial renal infarction [19], leads to a striking curtailment of fractional proximal tubular sodium and fluid reabsorption. The situation after unilateral nephrectomy also resembles that encountered during extracellular volume expansion, particularly when the latter is sustained over a longer time period [12,20].

The functional behavior of the remaining kidney in the present series of experiments is characterized by augmentation of SNGFR, an unchanged rate of absolute proximal tubular sodium reabsorption, and the delivery of larger than normal fractions of the filtrate into the loop of Henle and into the distal tubule. Thus, glomerulotubular balance, i.e., the parallel and proportional adjustment of proximal tubular sodium reabsorption in response to changes in the absolute rate of glomerular filtrate formation, is clearly not maintained in the remaining kidney after contralateral nephrectomy. In the present experiments, the disruption of glomerulotubular balance was associated with an unchanged filtration fraction, i.e., both SNGFR and glomerular blood flow increased proportionately. As a result, the peritubular protein concentration remained unchanged in clamped kidneys with unilateral nephrectomy despite the fact that SNGFR had increased significantly.

It is possible that the failure of proximal tubular sodium reabsorption to increase with the rise in the filtered sodium load is related to the fact that the peritubular protein concentration did not change with the rise in SNGFR. Evidence has been presented by others, notably by Windhager, Lewy, and Spitzer [21], Earley, Martino and Friedler [22], and by Brenner and Troy [23] that some states of glomerulotubular balance are partly maintained by an adjustment of the filtration fraction, changes in peritubular protein concentration, and the resulting modulation of the proximal tubular sodium transport system. The site of the mechanism affecting sodium reabsorption is thought to be the translocation of tubular reabsorbate from intercellular spaces into the peritubular capillaries, a process subject to control by the oncotic pressure within peritubular capillaries. According to this thesis, the increase in postglomerular protein concentration, proportional to the increment in SNGFR, plays a crucial and causal role in the maintenance of glomerulotubular balance.

Operation of this mechanism is clearly absent in cortical nephrons after contralateral nephrectomy. It appears that cortical renal blood flow increased in proportion to the rise of filtration rate in superficial nephrons and maintained the filtration fraction and absolute fluid and sodium reabsorption at constant levels. The situation here is similar to that encountered during chronic extracellular volume expansion [20]. The latter condition is characterized by a parallel increase in superficial SNGFR and of glomerular blood flow, such that filtration fraction and peritubular oncotic pressure remain unchanged. Again, glomerulotubular balance is not maintained since the absolute rate of proximal tubular sodium reabsorption remained unaltered despite a marked increase in the filtered sodium load.

Despite the similarities between the two experimental conditions—chronic saline-loading and unilateral nephrectomy—it is unlikely that the natriuresis observed in the present series of experiments was related to a proportionately larger increase in

extracellular fluid volume during the micropuncture experiments in ½ Nex rats than in control animals. This view is based on experimental results in which it was shown that the directly measured extracellular fluid volume was similar two hr after a moderate i.v. saline load in control and unilaterally nephrectomized rats [24]. Wong and Dirks also showed that volume expansion did not abolish the diuretic response of unilateral nephrectomy [17].

Several factors support the view that hemodynamic factors are involved in the reduction of proximal tubular sodium and fluid reabsorption observed after unilateral nephrectomy. First, we have observed that the arterial blood pressure level is moderately but significantly elevated after uninephrectomy. Others have made similar observations [25,26,27]. The origin of the blood pressure increase after nephrectomy is unknown. Although not ruled out, it is unlikely to be related to stimulation of the renin plasma angiotensin system since the renin activity has not been found changed after unilateral nephrectomy [28]. Furthermore, the acute reduction of the systemic blood pressure prior to the micropuncture experiment by an aortic clamp above the origin of the renal arteries to the control level reduced SNGFR, elevated the filtration fraction, and at the same time reestablished glomerulotubular balance. It is also relevant that Carriere, Wong and Dirks observed vasodilation in all regions of the remnant, reduced kidney (70-80% of the branches of the renal artery ligated) when the opposite kidney was removed [25]. Both an elevated blood pressure and local renal vasodilation would favor an increase in SNGFR and in glomerular blood flow. Consistent with this interpretation is our observation in ½ Nex kidneys of a moderate but significant elevation of the peritubular capillary pressure and of a reduction of the hydrostatic pressure difference between the proximal tubular lumen and that of peritubular capillaries. Such a reduction of the hydrostatic pressure gradient would also tend to curtail sodium reabsorption by reducing peritubular capillary fluid uptake.

It is not clear what possible role the redistribution of the glomerular filtrate to the superficial nephrons could have been in the observed diuresis after nephrectomy. Some reduction of deep nephron function is implied by the increase in superficial nephron GFR in the presence of an unchanged rate of whole kidney GFR. However, no direct information is available concerning either the properties of tubular sodium transport in deep juxtamedullary nephrons nor the effect thereupon of changes in GFR. In view of the observed similarity of filtration fraction values of the whole kidney and of superficial nephrons after nephrectomy it is unlikely that deep nephron filtration fraction was dramatically affected during the adaptive response to contralateral nephrectomy.

It should be emphasized that the mechanism underlying proximal tubular natriuresis 15 hr after contralateral nephrectomy may differ in several aspects from the situation encountered after acute nephrectomy [1,28], ablation of renal tissue [18], or renal infarction [19]. In some of these acute situations, natriuresis may occur with only a very moderate change, or even in the absence of an increase in SNGFR [17,28]. For instance, in acutely unilaterally nephrectomized rats, natriuresis results from diminished absolute rate of proximal tubular sodium reabsorption at unchanged rates of SNGFR, and the inability of distally located nephron segments to increase sodium reabsorption enough to prevent natriuresis [29]. Clearly, this situation differs from that encountered 15 hr after nephrectomy. Also, the increase in systemic blood pressure which is consistently observed immediately following exclusion of one kidney from the circulation is not always involved in the genesis of natriuresis immediately following contralateral nephrectomy: lowering of the arterial blood pressure by aortic constriction does not abolish the acute natriuresis immediately after nephrectomy [17,26,27]. Thus, participation of a humoral mechanism [30] in response to unilateral nephrectomy could play a role, particularly in those states in which sodium reabsorption is reduced but cannot be related to measurable changes in glomerular fluid delivery, changed aldosterone or antidiuretic hormone release, or to modification of peritubular oncotic and hydrostatic pressure.

A consideration of distal tubular function 15 hr after contralateral nephrectomy showed a pattern quite similar to that observed when a larger fraction of the filtrate enters this nephron segment [12,13]. With respect to fluid reabsorption, an increase in the absolute rate of distal tubular fluid reabsorption occurred but it was of insufficient magnitude to prevent development of a significant diuresis. Again, similar to the situation in animals undergoing saline diuresis, urinary fluid loss was significantly less than the amount of filtered water escaping proximal tubular reabsorption. Sodium reabsorption along the distal tubule, although augmented, is clearly insufficient to prevent enhanced sodium excretion into the final urine. If the situation were similar to that during extracellular volume expansion, an additional important factor promoting diuresis may be operative at the collecting duct level to inhibit tubular sodium reabsorption [31—33].

The situation concerning distal tubular sodium

handling is also similar to that after extracellular volume expansion [12,13]. With the delivery of increased quantities of fluid and sodium into the distal tubule, the normally observed decline in distal tubular sodium concentration along this nephron segment becomes attenuated or absent. Associated with these higher luminal sodium concentrations, sodium reabsorption increased significantly. Hence, distal tubular sodium reabsorption is significantly augmented as the sodium load is redistributed from proximal to distal nephron sites. However, the present experiments do not allow a critical assessment of the effects of contralateral nephrectomy *per se* on the intrinsic properties of distal tubular sodium transport since we have no data when the distal tubular epithelium is exposed to a normal sodium load after unilateral nephrectomy.

A consideration of our distal tubular potassium data indicates that tubular potassium concentrations remained unchanged despite the large increase in fluid delivery. As a consequence, net potassium secretion increased in proportion to flow rate. Again, this situation strikingly resembles that seen during the elevation of distal tubular fluid delivery after acute extracellular volume expansion [14]. The possible mechanisms underlying the marked kaliuresis resulting from enhanced distal tubular flow rate have been discussed in detail elsewhere [14]. The present observations emphasize the large capacity of the distal tubule to increase potassium secretion. We have not observed the involvement of the collecting duct epithelium in the secretory response of the kidney with respect to potassium but such nephron sites may be activated with more extensive removal of renal tissue [34]. Recent experiments by Schon, Silva and Hayslett [35] and Silva, Hayslett and Epstein [36] have implicated participation of the ATPase system in the response of remnant kidneys (¾ nephrectomized rats) to physiological potassium loads. These authors showed that a significant increase of Na-K activated ATPase occurs in the renal cortex and the renal medulla of such remnant kidneys, suggesting that this enzyme may be involved in the adaptation of remaining distal tubules to elevate their rate of potassium secretion.

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